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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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11/14/2003

Benjamin Levinson

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MORRISON & FOERSTER LLP
755 PAGE MILL RD
PALO ALTO, CA 94304-1018

EXAMINER

KRISHNAN, GANAPATHY

ART UNIT

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1623

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DELIVERY MODE

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/713,889	Applicant(s) LEVINSON ET AL.	
	Examiner Ganapathy Krishnan	Art Unit 1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 June 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2-5,8-31 and 34-37 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2-5,8-31 and 34-37 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>6/11/08</u> . | 6) <input type="checkbox"/> Other: _____ |

Art Unit: 1623

DETAILED ACTION

The amendment filed 6/11/2008 has been received, entered and carefully considered.

The following information provided in the amendment affects the instant application:

1. Claims 1, 6-7 and 32-33 have been canceled.
2. Remarks drawn to rejections under 35 USC 112, second paragraph, 102 and 103.

Claims 2-5, 8-31 and 34-37 are pending in the case.

The rejection of Claims 21, 23-28 and 31 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been overcome in view of applicants arguments and support in the specification.

The rejection of Claim 29 under 35 U.S.C. 102(b) as being anticipated by Goel et al (WO 97/05152; document cited in IDS of 10/3/2006) has been overcome in view applicants arguments. The prior art does not teach formulations comprising tin mesoporphyrins as instantly claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Art Unit: 1623

The rejection of Claims 2-5, 8-10, 22, 29-31 and 34-37 under 35 U.S.C. 103(a) as being unpatentable over Robinson (US Patent Pub. No. 2003/0100752) in combination with Drummond (Annals of New York Academy of Sciences, 1987, 514, 87-95) and Bettelheim et al (General, Organic and Biochemistry, 1998, page 596) is being maintained for reasons of record.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Applicants have traversed the rejection arguing that:

1. Robinson's teaching lists trillions of compounds.
2. Drummond indicates that cobalt protoporphyrin is an inhibitor in vitro but not in vivo.

The most potent compound is chromium protoporphyrin and the next most potent compounds are

Art Unit: 1623

manganese and tin protoporphyrins. Since these compounds are ultimately for pharmaceutical use one would select the most potent compound in vivo and not the one in vitro.

3. Protoporphyrins and mesoporphyrins are not interchangeable. According to Drummond tin protoporphyrin and tin mesoporphyrin are similar in vivo but when tin mesoporphyrin was administered to animals it was about ten fold more effective in lowering bilirubin production compared to tin protoporphyrin. These unpredictable results mean that tin mesoporphyrins and tin protoporphyrins are not interchangeable.

Applicants' arguments have been considered but are not found to be persuasive.

It is true that Robinson's teaching lists trillions of compounds. But based on the teachings of the secondary references one of skill in the art can recognize that the trail leads to the preference of tin as the central metal. Applicants state that the most potent compound is chromium protoporphyrin and the next most potent compounds are manganese and tin protoporphyrins. Since Drummond teaches that cobalt protoporphyrin is not an inhibitor in vivo the same result cannot be extrapolated to tin protoporphyrin. Applicants have not produced any teaching in support of this extrapolation. If cobalt protoporphyrin is not an inhibitor in vivo then one of skill in the art will not look at such a compound. One would look for the next best potent compound. According to Drummond one such compound is tin protoporphyrin. The genus now is very small based on the teachings of the prior art.

According to Drummond tin protoporphyrin and tin mesoporphyrin are similar in vivo but when tin mesoporphyrin was administered to animals it was about ten fold more effective in lowering bilirubin production compared to tin protoporphyrin. This result means that tin mesoporphyrins and tin protoporphyrins are interchangeable. Applicants are claiming tin

Art Unit: 1623

mesoporphyrin compounds. One of skill in the art looking for tin mesoporphyrin compounds on reading the teaching of Drummond as stated above will certainly choose tin as the central metal because according to Drummond (and admitted by the applicants) it is tin mesoporphyrin that is more potent when administered to animals (in vivo). This teaching by Drummond may look like unexpected results but they are results that actually strongly point to tin mesoporphyrin as the compound of choice. This fact will certainly be recognized by one of skill in the art. So, the extremely large genus of Robinson is now reduced to a genus of three compounds with central metal atoms being cobalt manganese and tin, out of which tin stands out as the metal of choice based on the teaching of Drummond. This teaching also makes the two porphyrins interchangeable.

Bettelheim in general teaches that amino acids exist as zwitterions and are polar. This renders them water soluble. From this and the teaching of Robinson, one of ordinary skill in the art will recognize that complexing the tin-mesoporphyrins of Robinson with amino acids will enhance the solubility of the mesoporphyrins. Robinson also teaches the use of aqueous solutions of the porphyrins for administration.

Based on the teachings of the prior art above, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make tin mesoporphyrins comprising amino acid residues complexed to the porphyrins, their compositions and use them in a method for treating heme metabolism disorders, hyperbilirubenemia and psoriasis, with a reasonable amount of success since structurally close analogs and their use for the same method of treatment is seen to be taught in the prior art.

Art Unit: 1623

One of ordinary skill in the art would be motivated to make tin mesoporphyrins and use them in a method of treatment as instantly claimed because the structurally analogous tin protoporphyrins, as taught by Drummond, are not toxic and complexing amino acids to the porphyrins would enhance their aqueous solubility.

Even though Drummond teaches protoporphyrins, Robinson's teaching embraces both proto and mesoporphyrins. Proto- and mesoporphyrins are known in the art and are recognized as interchangeable because of their structural similarity. Hence one of ordinary skill in the art would reasonably expect tin mesoporphyrins as instantly claimed to have the same or substantially similar beneficial therapeutic effects (in fact, Drummonds teaching shows that it is more potent). One of skill in the art would also extend the teachings of the prior art to making tin mesoporphyrins in order to look for more active compounds.

The rejection of Claims 11-28 and 31 under 35 U.S.C. 103(a) as being unpatentable over Niedballa et al (US 5,275,801) is being maintained for reasons of record.

Applicants have not provided any substantive arguments except stating that in view of the changes in activity as stated in their arguments above and the Examiner not providing any reason or motivation for making any change to Niedballa the rejection should be withdrawn.

Applicants' arguments have been considered and are not found to be persuasive.

The instant claims are drawn to a method preparation of the tin mesoporphyrin compounds. Hence, the activity of the final product has no bearing on the process of making it.

Niedballa et al teach a general method of making a water-soluble porphyrin complex (col. 13, line 34 through col. 14, line 12) wherein a porphyrin core structure of formula (I') (col. 7),

Art Unit: 1623

comprising amino acid residues is obtained by mixing the core structure (I') with amino acid; complexing with metal ions, which includes tin (col. 13, lines 32-43). Secondary reactions like hydrogenation, esterification, and alkylations are all performed according to literature processes known to one of skill in the art (col. 11, lines 3-7). The use of basic solutions like sodium hydroxide in the steps where amino acids are used in a specific form is taught by Niedballa (col. 14, lines 32-39) as well as the use of metal dichlorides for the introduction of the desired metal (col. 13, line 62). The general method of Niedballa results in a solid or pharmaceutically acceptable liquid. Vacuum drying is used to dry the product (col. 14, lines 16-17). These are all steps that one of skill in the art will recognize to be useable for making the products as instantly claimed. Niedballa also teaches that secondary reactions like hydrogenation, esterification, and alkylations are all performed according to literature processes known to one of skill in the art. One of ordinary skill in the art would be motivated use the method of Niedballa since it is a general method applicable to the porphyrin core and gives high yields. Since the prior art method gives the desired product in high yields one of skill in the art would prefer to use the same method with minor changes if needed.

Conclusion

Claims 2-5, 8-31 and 34-37 are rejected

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

Art Unit: 1623

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1623

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shaojia Anna Jiang, Ph.D./
Supervisory Patent Examiner, Art Unit 1623

/Ganapathy Krishnan/
Examiner, Art Unit 1623